Vincent W. Ing

The Etiology and Management of Leukopenia

SUMMARY

Leukopenia is an abnormal reduction of circulating white blood cells, especially the granulocytes. The term leukopenia is often used interchangeably with neutropenia. It may result from reduced production of white blood cells or increased utilization and destruction, or both. Infection, drugs, malignancy, megaloblastosis, hypersplenism and immunoneutropenia are responsible for most cases of neutropenia. Primary neutropenia is very rare. Sometimes, particularly in children, primary neutropenia is hereditary and may be associated with other developmental defects. The major danger of neutropenia is the risk of infection. Management requires identification of the cause and effective antimicrobial therapy, especially when serious systemic infection is present. (Can Fam Physician 1984; 30:1835-1839.).

SOMMAIRE

La leucopénie est une diminution anormale de la quantité de leucocytes circulants, affectant surtout les granulocytes. On confond souvent le terme leucopénie avec neutropénie. La neutropénie peut soit réduire la production efficace des globules blancs, soit augmenter leur utilisation et leur destruction, ou les deux. Infection, médicaments, tumeur maligne, mégaloblastose, hyperplénisme et immunoneutropénie sont responsables de la plupart des cas de neutropénie. La neutropénie primaire est très rare. Parfois, surtout chez les enfants, la neutropénie primaire est héréditaire et associée à d'autres anomalies congénitales. Le principale menace engendrée par la neutropénie est le risque d'infection. Le traitement requiert l'identification de la cause et une thérapie antimicrobienne, surtout en présence d'une infection systémique grave.

Dr. Ing is an assistant professor in the Department of Medicine at Dalhousie University, Halifax, and an attending physician at the Halifax Infirmary and Victoria General Hospital, Halifax, NS. Reprint requests to: Suite 635, 5991 Spring Garden Rd., Halifax, NS. B3H 1Y6.

LEUKOPENIA IS an absolute reduction in circulating white blood cells below the lower limit of normal values. Technically, it includes neutrophils, monocytes and even lymphocytes. In clinical practice, it is practically synonymous with neutropenia.

Agranulocytosis implies a much more serious deficit. The lowest normal concentration of neutrophils is about 1,500-1,800 per mm^3.[1] This minimum number may vary among different ethnic groups; lower neutrophil counts have been recorded for blacks in the U.S. and Africa.[2, 3]

There is a rough correlation between the degree of neutropenia and the risk of bacterial infection. An absolute count of 500-1,000 per mm^3 is associated with moderately increased risk. A count below 500 per mm^3 (i.e., agranulocytosis) that persists for more than a few days, is invariably associated with serious infection.

The risk of infection may be modified considerably by the presence of monocytosis. In general, monocytes have less phagocytic and bactericidal activity. Their rate of mobilization to sites of inflammation is also less efficient.[4]

Granulocyte Kinetics

In normal adults, granulocyte production[5] takes place primarily in the bone marrow. The life history of the granulocytes can be separated into bone marrow, blood and tissue phases. In the bone marrow phase, the myeloblasts, promyelocytes and myelocytes (progeny of the committed stem cell CFU), constitute the mitotic compartment. They are all capable of cell divisions. Metamyelocytes, band and segmented neutropils, all incapable of cell divisions, constitute the maturations storage compartment. The size of this compartment is about seven to 13 times that of the peripheral blood pool. It has been estimated to be between five and 9×10^9 cells/kg Bwt.[5] In the peripheral blood pool, the granulocytes establish an efficient equilibrium between the circulating blood granulocyte pool (CGP) and the marginal granulocyte pool (MGP). In an emergency, rapid reinforcement of CGP can be achieved within a short time by a preferential shift from the MGP. The granulocytes circulate in the peripheral blood for about ten hours before making an unidirected entry into the tissue phase.

Functional Classification Of Neutropenia

Neutropenia may result from reduced effective production of white blood cells, increased utilization or destruction, or all of these.[6,7] Reduced delivery of mature neutrophils from the bone marrow may be related to reduced myeloid proliferation in the marrow or ineffective granulocytopoiesis. The major mechanisms for an excessive loss of neutrophils from the peripheral blood are: accelerated migration into the tissue in association with infection or inflammation; reduced survival due to a maturation defect, increased reticuloendothelial system (RES) activity or cell damage by leucotoxin, or an abnormal transient or prolonged shift into the marginal pool.

Type 1:
Reduced production with myeloid hypoplasia

Myeloid proliferation is suppressed, resulting in shrinkage of the marrow storage pool. The neutrophil survival is relatively unaffected. However, the total turnover is reduced. Biopsy of the bone marrow may demonstrate fibrosis, dysplasia, leukemia or malignant cell infiltration, and other morphologic aberrations, in addition to bone marrow hypoplasia.

Type 2:
Ineffective granulocytopoiesis

Intramedullary death of myeloid precursors is a dominant feature. Despite an apparent marrow myeloid hyperplasia, the storage pool is reduced, and fewer cells are released into the peripheral blood. The best example is the myeloid maturation defect due to vitamin B_{12} deficiency. Megaloblastosis is a common feature, along with significant elevation of serum lactic dehydrogenase.[8]

Type 3:
Reduced granulocyte survival

An acceleration in the consumption of granulocytes in the peripheral blood stimulates an increase in the effective granulocytopoiesis.[9] Neutropenia develops when the depletion rate exceeds the production rate. The bone marrow is hypercellular, with increased myeloid immaturity. Leukocyte reserve pools are reduced. The turnover rate is markedly increased, and the neutrophil survival is shortened. This condition may be due to leukocyte antibody or toxin,[10] hyperactivity of the reticuloendothelial system or excess splenic sequestration.

Type 4:
Combination granulocytopenia

This is probably the mechanism which most commonly produces neutropenia. The best example is acute leukemia with sepsis. The effective granulocytopoiesis is severely restricted to begin with, and sepsis further promotes excessive peripheral destruction of granulocytes.

Type 5:
Pseudoneutropenia

Pseudoneutropenia[11] is an apparent neutropenia, resulting from a shift in equilibrium towards the marginal granulocyte pool. Occasionally, an increase in the size of the bone marrow storage pool, due to an impaired release of marrow neutrophils, may also be responsible. The total granulocyte pool remains normal. Leukocyte kinetics are unaffected. Pseudoneutropenia usually is transient in association with virema, hypersensitivity state or splenic and hepatic congestion. It also may occur in familial or chronic form.

Clinical Approach To Neutropenia

Neutropenia may be present as an isolated hematologic abnormality or in association with anemia and/or thrombocytopenia. The mode of clinical presentation may vary considerably. Neutropenia may be an incidental finding or overshadowed by other clinical disturbances. It is essential to elicit a careful history, with specific reference to drugs, exposure to toxic compounds, possible genetic predisposition, nutritional state and significant constitutional symptoms, such as fever and weight loss. Physical examination should be performed with keen attention to lymphadenopathy, spleen and liver evidence suggesting a multiple system disease or malignancy. In dealing with a case of mild and asymptomatic neutropenia, it is reasonable to postpone all investigations for one to two weeks and repeat the hemogram to assure that neutropenia is not an artifact produced by electronic counters. Other causes of spurious neutropenia include clumping in the presence of paraproteinemia, and counts done on aged blood. However, symptomatic neutropenia, agranulocytosis and pancytopenia deserve prompt attention.

The laboratory investigations needed to identify the cause of neutropenia include complete blood counts, bone marrow aspiration and trephine biopsy, liver function tests and lactic dehydrogenase. Studies pertaining to granulocyte kinetics and turnover, ability of phagocytosis and migration are usually feasible only in granulocyte research centres. Indeed, in most cases, these studies are not essential for the clinical diagnosis of neutropenia. In specific cases, marrow granulocyte reserves can be assessed by using 200 mg of intravenous hydrocortisol and measuring the peak neutrophil concentration in three to four hours.[12]

In clinical practice, most cases of neutropenia can be accounted for by several pathologic entities. These include infection, drugs, malignancy, hypersplenism, megaloblastosis and immunoneutropenia.

Infection

Many acute systemic viral or rickettsial infections produce neutropenia. The characteristic pattern is that which occurs with infectious hepatitis[13] or mononucleosis.[14] Leukopenia develops during the first two days and may persist for three to seven days, a time which corresponds to the period of acute viremia and virally-induced leukocyte damage resulting in excessive peripheral margination and utilization. Atypical lymphocytes are often observed during the same period. Toxic cytoplasmic granulation and Dohle bodies frequently appear in the neutropenia phase. Usually, the granulocyte count returns by the tenth to the fourteenth day. Other infectious diseases often associated with neutropenia include rubella, smallpox, chickenpox and measles.[15]

Agranulocytosis may occur in association with an overwhelming infection in a previously healthy individual. Mild to moderate cases of neutropenia are often associated with bacillary dysentery, typhoid and paratyphoid fever and brucellosis,[15] although the responsible mechanism is poorly understood.

Drugs

Due to the frequent use of multiple drugs, it can be difficult to identify the responsible drug. Often, the clinician is forced to made an educated guess, based upon his analysis of the patient's drug record and the temporal relationship of the drugs to the onset of neutropenia, as well as upon his knowledge of the pharmacological action and side effects of the drugs in question. In addition, the disease for which the drugs are used may well contribute to the development of neutropenia.

Two categories of drug-induced neutropenia have been recognized. These are predictable reactions and idiosyncratic reactions.

Predictable reactions: If given in sufficient doses, the drugs in this category will consistently cause neutropenia. The best examples are cancer chemotherapeutic agents. They act mainly by interfering with cell production, either by directly injuring the stem cell or mitotic compartment of the bone marrow, or by slowing cell division by blocking DNA strand duplication, interfering with the purine or pyrimidine metabolism, disrupting the microtubules of the mitotic spindle, or interfering with RNA formation and the translation and transcription processes. The neutropenia is dose-related. There is usually a delay before neutropenia appears. The length of the delay is related to the size of marrow neutrophil reserve. In a previously healthy marrow, a delay of eight to 14 days can be expected, even after complete suppression of cell production.

Idiosyncratic reactions: These[16, 17] tend to be more prevalent among women, the elderly, or patients with a strong history of allergies. In general, idiosyncratic reactions can be divided into two categories—slow or delayed onset and abrupt onset neutropenia.

The phenothiazine derivatives are implicated more frequently in the etiology of slow onset neutropenia than any other drug.[18] This adverse reaction is dose dependent, rarely occurring within two weeks or after 90 days of drug administration. At times, agranulocytosis may appear. Not infrequently, however, the neutrophil concentration may stabilize at a reduced level or may even return towards normal when the drug continues to be administered. The bone marrow is aplastic or hypoplastic when neutropenia has developed. It is believed that bone marrow suppression is due to drug inhibition of DNA synthesis.[18]

In some cases, abrupt onset neutropenia rapidly follows repeated or intermittent exposure to a drug. The mechanism is often unclear but is presumed to be immunologically mediated. Drug-hapten antibody reaction[17] has been proposed as a cause in some situations. Eosinophilia and monocytosis may be present, along with bone marrow myeloid hyperplasia. Following the cessation of drug therapy, bone marrow function recovers in a few days. Occasionally, however, the neutropenia may be irreversible. In specific situations, genetic abnormality might predispose a patient to a drug reaction. The increased incidence of adverse effects with sulfasalazine in individuals who are slow acetylators is an example of such genetic susceptibility.[19]

The drugs that most clinicians recognize as being associated with neutropenia include phenothiazine, diuretics, antithyroid agents, nonsteroidal anti-inflammatory agents, certain antibiotics and analgesics. We must recognize that all drugs have the potential to induce an idiosyncratic granulocytopenia.

Malignancy

Neutropenia may be associated with all hematological or non-hematological malignancies. In most cases, there is clear evidence of disturbance of all bone marrow elements. In selected cases of acute leukemia, neutropenia might be the only abnormality discovered on a routine hemogram. The pressence of a frank leukoerythroblastic picture in the absence of significant splenomegaly should arouse serious suspicion of bone marrow infiltration by tumor cells.

Hypersplenism

Leukopenia occurs with splenomegaly in many diseases, such as cirrhosis with portal hypertension, lymphoma, sarcoidosis and Felty's syndrome. The usual picture is a modest reduction of all blood elements. The bone marrow cellularity is often increased with normal maturation sequence. The survival of neutrophils is, however, shortened.

Megaloblastosis

This pathologic process[20] should be seriously entertained in the presence of poor nutritional state, anorexia, alcoholism, senility, neurological deficits, and chronic diarrhea. In most cases, pancytopenia is present, although isolated neutropenia might be the presenting hematological abnormality. Laboratory abnormalities that might provide clues to this process include high MCV, the presence of hypersegmented neutrophils, oval macrocytes, and high lactic dehydrogenase. The common etiologic deficiency is folic acid, due either to nutritional deficiency or a drug (e.g., phenytoin)[21] which interferes with its metabolism. Vitamin B_{12} deficiency results in an identical pathological state.

Immunoneutropenia[22]

Neutropenia is present in over 50% of patients with disseminated lupus erythematosus.[23] The presence of circulating leukoagglutinins, in conjunction with splenomegaly, can often be demonstrated. Seldom is immunoneutropenia severe enough to increase the patient's susceptibility to infection. Leukocyte auto-antibodies have also been associated with other connected tissue diseases, such as rheumatoid arthritis and Felty's syndrome. Rarely, auto-antibodies may occur in an idiopathic form, similar to the way in which autoimmune hemolytic anemia or thrombocytopenia appear.

Uncommon neutropenis disorders[24, 25]

Pediatric: Several clinical syndromes have been associated with neutropenia. Some are transmitted as an autosomal recessive or dominant trait. Others appear to be sex-linked recessive disorders. The bone marrow cellularity varies among these syndromes, indicating that several mechanisms are responsible for the granulocytopenia. Many of these neutropenic patients also demonstrate other developmental disorders (i.e., thymic aplasia, B cell dysfunction, or bone growth abnormalities). The risk of infection varies greatly. Even among those with recurrent bouts of infection, life can be lengthened significantly with aggressive antibiotic therapy.

Adult: Benign familial neutropenia[26] is transmitted as an autosomal dominant trait. Affected patients are often healthy, showing moderate monocytosis and eosinophilia. Bone marrow studies are usually unremarkable. In recent years, the definition of this syndrome has been broadened to include several large ethnic groups with genetically determined neutropenia.

With non-familial chronic idiopathic neutropenia[27] the bone marrow is normal or moderately hypercellular and contains no segmented neutrophils. In general, the risk of infection is not significant. A modest monocytosis is usually present.

Chronic hypoplastic neutropenia[28] is a rare disorder with significant marrow suppression and a high risk of bacterial infection recurring. There is no hereditary pattern. Some patients have an associated thymic disorder or hypogammaglobulinemia. Absolute monocytosis is unusual.

Some cases of cyclic neutropenia[29] appear to be transmitted as an autosomal dominant trait, while others have no significant hereditary basis. The usual history is that at intervals of every two or three weeks patients demonstrate fever lasting for several days, as well as neutropenia which lasts for three or four days. Studies indicate the disorder may be the result of periodic stem cell failure.[35]

Pseudoneutropenia is another type of adult neutropenia. Acute cases of neutropenia have occasionally been observed in association with anaphylaxis, leukophoresis or hemodialysis. When neutrophils adhere to the filter, they release a labile factor which induces vascular margination. Chronic forms may be present with prolonged malnutrition. The neutropenia might represent redistribution of granulocytes within various compartments.

Management

The treatment[30] of neutropenia depends on its etiology, severity and the estimated risk. In situations where the etiological factor can be identified and rectified (e.g., drugs, folic acid deficiency), treatment should be instituted without delay. The risk of infection depends upon a complex interrelationship of lymphocytes, neutrophils and macrophages, cellular and circulating immunological defense, along with physical barriers which normally provide protection against infecting organisms. Any qualitative or quantitative defect in one of these factors may predispose the patient to infection.

When neutropenia is severe and prolonged (e.g., in cases of acute leukemia), a major problem is recognizing the infection. Due to the paucity of neutrophils, purulent exudates are scanty and clinical signs may be minimal. Other significant factors promote infection. In addition to quantitative deficiency of neutrophils, their bactericidal activity is often diminished. In addition to their myelosuppressive activity, antineoplastic drugs also have deleterious impact on functions such as cytotoxicity mediated by leukocytes. It has been demonstrated that doxorubicin, vincristine and other such drugs can decrease leukocyte-mediated, antibody-dependent cellular cytotoxicity (ADCC) and natural killer cytotoxicity (NKC) against viral infected target cells.[31] Mechanical barriers, which represent an important limiting factor to colonization and infection, frequently are disrupted by well intentioned but iatrogenic measures (e.g., oropharyngeal and gastrointestinal ulcerations due to cancer chemotherapy, urethral catheterization and indwelling venous catheters).

Treating such a complicated case requires intense nursing care and constant and keen observation for the slightest evidence of infection. If fever or tangible evidence of infection develops, suitable blood, urine and throat cultures should be obtained, and then antibiotics must be given, unless there is an obvious noninfectious cause. To provide adequate bactericidal coverage, combination antibiotics should be used. Most centres use an aminoglycoside plus antipseudomonal penicillin or cephalosporin. These agents are continued until the results of blood cultures and sensitivity tests are known, at which time the antimicrobial program may be readjusted if necessary. The antibiotics should be continued for at least three days after the patient has become afebrile. When there is obvious clinical deterioration or persistent fever after seven days of antimicrobial therapy, the clinician must completely reassess the patient, keeping in mind the possibility of an opportunistic infection or abscess.

In selective cases, specific diagnostic measures such as open lung biopsy or bronchoscopy may be required, in addition to blood cultures. When no concrete evidence of the etiological agent can be secured, a trial of amphotericin, ketoconazole or even a systemic antiviral agent, is appropriate. Although the effectiveness of granulocyte transfusion has been well established, in general it should be considered only when there is fulminant infection and the response to antibiotics has been suboptimal. Granulocyte transfusion on a prophylactic basis is not recommended, in view of the risk of cytomegalovirus infection.[32]

In cases of chronic neutropenia, bacterial infections are usually a less serious problem. In specific situations where the etiologic factor is primarily hypersplenism or immunoneutropenia, splenectomy may be beneficial.

Prophylaxis of infection

Different measures have been studied, with the intention of either reducing bacterial infection or promoting granulocyte functions. Reverse isolation, which was quite popular for many years, has been found to have no specific value. The efficacy of a germ-free protective environment, especially when used with prophylactic antibiotics, has been established. However, due to its prohibitive cost and the psychological impact on the patient, it is seldom used.[30] Prophylactic antibiotic programs have remained controversial. In our centre, Septra DS tablets, one bid are used only for compromised patients, such as those with acute leukemia who are undergoing induction chemotherapy.

Androgen therapy combined with small doses of corticosteroid for three to four months has achieved moderate but unpredictable success in promoting production in cases of nonmalignant myeloid hypoplasia. Recently, lithium carbonate has been discovered to enhance proliferation of human granulocytic colonies in vitro. In some centres, lithium carbonate 900 mg per day is used during induction chemotherapy in acute leukemia.[33] In my experience, however, its effects have been rather unimpressive.

Bone marrow transplantation

In recent years, allogeneic bone marrow transplantation has become an established modality for the treatment of aplastic anemia, immunodeficiency states and acute leukemia.[34] By restoring the normal hematological function, the bone marrow graft represents an indirect adjuvant measure in the management of infection. It takes several weeks for the donor's graft to become firmly established. Until then, the recipient is at great risk of serious and sometimes even fatal infection. ◉

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